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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 209/34, 209/38, 491/113, A61K 31/475 — A1

(11) International Publication Number: WO 94/29272

(43) International Publication Date: 22 December 1994 (22.12.94)

(21) International Application Number: PCT/SE94/00448

(22) International Filing Date: 13 May 1994 (13.05.94)

(30) Priority Data:
9302080-8 16 June 1993 (16.06.93) SE

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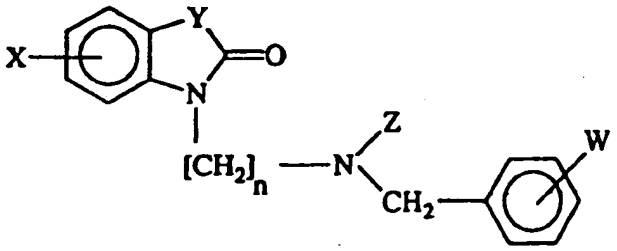
(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 1-SUBSTITUTED ISATIN AND OXINDOLE DERIVATIVES AS INHIBITORS OF ACETYLCHOLINESTERASE



(1)

(a) (b)

(57) Abstract

The present invention relates to novel compounds having general formula (1) wherein n is 3, 4, 5, 6 or 7; X represents one or more substituents independently selected from hydrogen, lower alkyl, aryl, lower alkoxy, halogen, trifluoromethyl, nitro, -NHCOR where R is lower alkyl or aryl, $-NR_1R_2$ where R_1 and R_2 are independently hydrogen or lower alkyl or together form a ring, or cycloalkyl, cycloalkenyl or bicycloalkyl either optionally further substituted by lower alkyl; Y is (a) or (b) where R_3 and R_4 are independently hydrogen, lower alkyl, lower alkoxy or together form a cyclic acetal; Z is lower alkyl; and W represents one or more substituents independently selected from hydrogen, lower alkyl, lower alkoxy or halogen; stereo and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof having therapeutic activity, intermediates for their preparation, processes for their preparation, pharmaceutical formulations containing said compounds and medicinal use of said compounds.

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1-Substituted Isatin and Oxindole Derivatives as Inhibitors of Acetylcholinesterase

Field of the invention

The present invention relates to novel compounds having therapeutic activity, intermediates for their preparation, processes for their preparation, pharmaceutical formulations containing said compounds and medicinal use of said compounds.

Background of the invention

A major characteristic of Alzheimer's Disease (Senile Dementia, SDAT) is a marked central cholinergic dysfunction. This cholinergic deficit has been reported to correlate with cognitive impairment (P.T. Francis et al, New Engl. J. Med., 1985, 313, 7). Various attempts to increase central cholinergic activity and thereby reverse the cognitive deficits have, to date, met with only limited success.

There is some evidence that use of the alkaloid physostigmine can, in some cases, be marginally beneficial, but the use of this compound in the clinic is compromised by a low therapeutic ratio, a short half-life and poor bioavailability. The cholinesterase inhibitor, 9-amino-1,2,3,4-tetrahydroacridine (THA) has been reported to be of therapeutic value in the treatment of a small group of patients with SDAT (W.K. Summers et al, New Engl. J. Med., 1986, 315, 1241). Further clinical trials of THA have produced some encouraging results but have been hampered by the association of this drug with certain toxic side effects.

Other compounds structurally related to either physostigmine or THA have been reported and are the

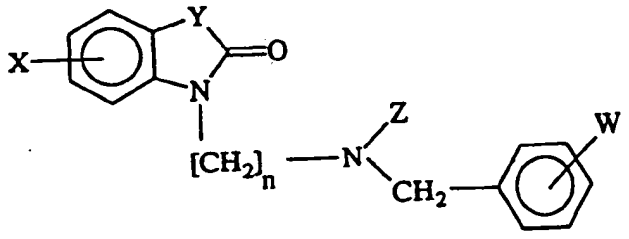
subject of ongoing investigations.

There remains an urgent need for a safe and clinically effective drug for the symptomatic treatment of Alzheimer's Disease and related conditions.

The present invention

A primary objective of the present invention is to provide structurally novel compounds which by virtue of their pharmacological profile enhance central cholinergic function and are of value in the treatment of the cognitive dysfunctions which may be associated with ageing or with conditions such as Alzheimer's Disease, Senile and related Dementias, Parkinson's Disease, Down's Syndrome and Huntington's Chorea. This utility is manifested, for example, by the ability of these compounds to inhibit the enzyme acetylcholinesterase. Further, the compounds of this invention are, in general, highly potent and selective, have an improved duration of action and are, in general, less toxic than hitherto known compounds.

The present invention relates to a compound having the general formula (1)



(1)

wherein:

n is 3, 4, 5, 6 or 7;

X represents one or more substituents independently selected from hydrogen, lower alkyl, aryl, lower alkoxy,

halogen, trifluoromethyl, nitro, -NHCOR where R is low r alkyl or aryl, $-NR_1R_2$ where R_1 and R_2 are independently hydrogen or lower alkyl or together form a ring, or cycloalkyl, cycloalkenyl or bicycloalkyl either optionally further substituted by lower alkyl;

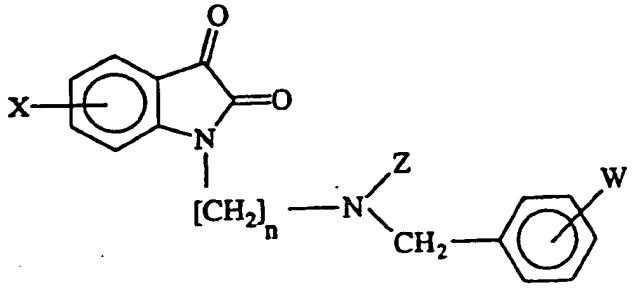
Y is $>CO$ or $>CR_3R_4$ where R_3 and R_4 are independently hydrogen, lower alkyl, lower alkoxy or together form a cyclic acetal;

Z is lower alkyl;

and W represents one or more substituents independently selected from hydrogen, lower alkyl, lower alkoxy or halogen.

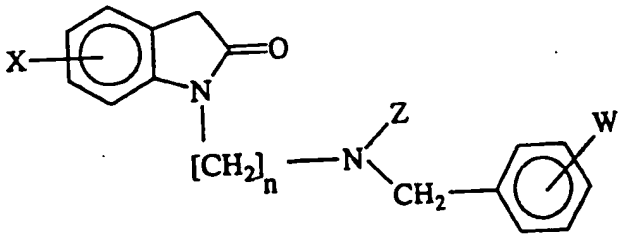
Stereo and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof are also part of the invention.

Preferred embodiments of this invention relate to compounds having the general formula (2)



(2)

wherein n, X, W and Z are as previously defined above; or to compounds having the general formula (3)



(3)

wherein n, X, W and Z are as previously defined above.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof such as for instance hydrates.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "lower alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said lower alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

Unless otherwise stated or indicated, the term "cycloalkyl" denotes a cyclic alkyl group having a ring size from C_3 to C_7, optionally additionally substituted by lower alkyl. Examples of said cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl and cycloheptyl.

Unless otherwise stated or indicated, the term "cycloalkenyl" d notes a cyclic alkenyl group having a ring size from C_3 to C_7, optionally additionally substituted by lower alkyl. Examples of said cycloalkenyl

include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, methylcyclohexenyl and cycloheptenyl.

Unless otherwise stated or indicated, the term "lower alkoxy" denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms. Examples of said lower alkoxy include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and straight- and branched-chain pentoxy and hexoxy.

Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

Unless otherwise stated or indicated, the term "aryl" denotes a phenyl, furyl or thienyl group in which the ring is optionally further substituted by lower alkyl, lower alkoxy or halogen.

Unless otherwise stated or indicated, the term "bicycloalkyl" denotes a bicyclic alkyl group having a size from C_6 to C_9, optionally additionally substituted by lower alkyl. Examples of said bicycloalkyl include bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl and bicyclo[2.2.3]nonyl.

Unless otherwise stated or indicated, the term "cyclic acetal" denotes a cyclic acetal group having a ring size from C_5 to C_7. Examples of said cyclic acetal includ 1,3-dioxolanyl and 1,3-dioxanyl.

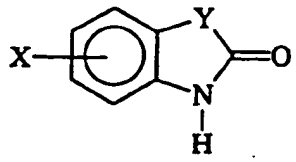
Preferred compounds according to the invention are those of general formula (2) or general formula (3) in which:
n is 4, 5 or 6
W is hydrogen or F, especially 4-F,
and X is low r alkyl, especially m thyl or ethyl, lower alkoxy, esp cially methoxy or ethoxy, cycloalkyl, especially C_5 to C_7 cycloalkyl, F, aryl, especially

phenyl, or $-NR_1R_2$, especially 1-pyrrolidinyl or 1-piperidinyl. More preferred compounds according to the invention are those of general formula (2) or general formula (3) in which the X substituent is at the 5-position.

Among the most preferred compounds of formula (1) according to the present invention are:
1,3-dihydro-1-(4-(N-ethyl-N-phenylmethylamino)butyl)-2H-indol-2-one;
5-cyclohexyl-1,3-dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-2H-indol-2-one;
5-cyclohexyl-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione;
1,3-dihydro-1-(5-(N-ethyl-N-(4-fluorophenyl) methylamino)pentyl-2H-indol-2-one;
5-cyclohexyl-1-(4-(N-ethyl-N-phenylmethylamino)butyl)-1H-indole-2,3-dione;
1-(4-(N-ethyl-N-phenylmethylamino)butyl)-5-phenyl-1H-indole-2,3-dione;
1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-5-(1-piperidinyl)-1H-indole-2,3-dione;
5-cyclohexyl-1,3-dihydro-1-(4-(N-ethyl-N-phenylmethylamino)butyl)-2H-indol-2-one;
1,3-dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-5-phenyl-2H-indol-2-one;
1,3-dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-5-methoxy-2H-indol-2-one;

and pharmaceutically acceptable acid addition salts or solvates thereof.

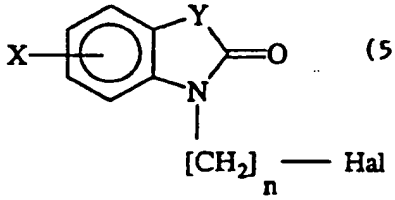
The present invention also relates to processes for preparing the compound having formula (1). Said compound may be prepared by treating a compound of the general formula (4)



(4)

wherein X and Y are as defined above,

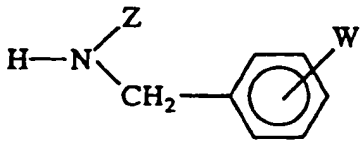
with a 1,n-dihaloalkane to obtain a compound of th general formula (5)



(5)

wherein X, Y and n are as defined above and Hal is halogen,

whereafter the compound of the general formula (5) is reacted with a compound of the general formula (6)



(6)

wherein W and Z are as defined above.

The process can be achieved, for example, by treating a compound of structur (4) with a 1,n-dihaloalkane, in a suitable solvent such as toluene or 3-methyl-2-butanone or acetonitrile or ac tone r dimethylsulphoxide or

dimethylformamid in th presence of a base such as triethylamine or anhydrous potassium carbonate. Such reaction should be conducted at a suitable temperature, normally between 0°C and 100°C, optionally in an inert atmosphere. Some compounds of type (5) are known in the literature. The intermediate (5) may either be isolated and purified and characterised using standard techniques or else may be reacted in a crude form with a compound of structure (6). Such reaction is preferably conducted in a suitable solvent such as dichloromethane or dimethylformamide in the presence of a base such as triethylamine or anhydrous potassium carbonate or an excess of compound (6), optionally with the addition of a catalytic amount of potassium iodide. The reaction should be conducted at a suitable temperature, normally between 0°C and 100°C, optionally in an inert atmosphere. The required product (1) may then be isolated and purified and characterised using standard techniques. In the case of products wherein Y represents an acetal or cyclic acetal group, the corresponding products wherein Y is >CO can be subsequently prepared by acid-catalysed hydrolysis in a manner that will be readily appreciated by one skilled in the art of organic synthesis.

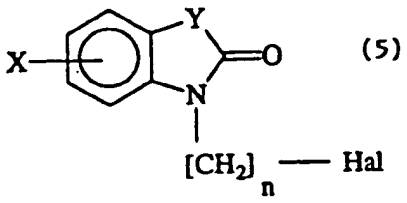
Compounds of structure (4) wherein Y is >CO are known as isatins (systematic name 1H-indole-2,3-diones). The isatins of structure (4) are, depending on the nature of the substituent(s) X, either compounds which have been previously described in the literature, or compounds which can be prepared by the straightforward application of known methods. The Sandmeyer procedure (Organic Syntheses, Coll. Vol. I., p 327), in which an aniline, chloral hydrat and hydroxylamine are reacted together to give an int rmediate isonitrosoacetanilid which is then

cyclised to the isatin on treatment with strong acid, is a particularly useful method.

Compounds of structure (4) in which Y is $>CH_2$ are known as oxindoles (systematic name 1,3-dihydro-2H-indol-2-ones). The oxindoles of structure (4) are, depending on the nature of the substituent(s) X, either known compounds or compounds which can be prepared using known methods. The Gassman reaction (P.G. Gassman et al, J.Amer.Chem.Soc., 1974, 96, 5508 and 5512) constitutes a well-known and general synthesis of oxindoles.

Compounds of structure (4) wherein Y represents an acetal or cyclic acetal can be prepared from compounds of structure (4) wherein Y is $>CO$ by the straightforward application of known methods in a manner that will be readily understood by those skilled in the art.

Thus, the present invention also refers to some new intermediates of formula (5), namely:



(5)

wherein n is 5, 6 or 7 and X, Y and Hal are as defined above, with the proviso that when n is 5 and Y is $>CO$, X is not H.

In certain circumstances it is advantageous to prepare oxindoles from the corresponding isatins. This

transformation may be achieved using such known methods as:

a) catalytic hydrogenation/hydrogenolysis;

b) formation of the corresponding 3-hydrazone followed by reductive elimination under basic conditions (Wolff-Kischner procedure);
or

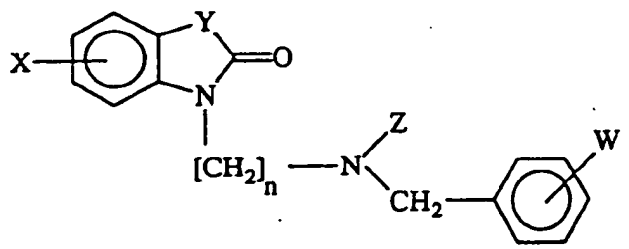
c) formation of the corresponding 3-dithioacetal followed by reduction using Raney nickel or nickel boride.

Method (c) represents a preferred process for the conversion of certain isatins (1;Y is >CO) or (4;Y is >CO) into the corresponding oxindoles (1;Y is $>CH_2$) or (4;Y is $>CH_2$) respectively.

The present invention also relates to pharmaceutical formulations containing a compound according to claim 1.

Another object of the present invention is a compound according to claim 1 for use in therapy.

Still another object of the present invention is the use of a compound having the general formula (1)



(1)

wherein:

n is 3, 4, 5, 6 or 7;

X represents one or more substituents independently selected from hydrogen, lower alkyl, aryl, lower alkoxy, halogen, trifluoromethyl, nitro,
-NHCOR where R is lower alkyl or aryl,
$-NR_1R_2$ where R_1 and R_2 are independently hydrogen or lower alkyl or together form a ring,
or cycloalkyl, cycloalkenyl or bicycloalkyl either optionally further substituted by lower alkyl;

Y is $>CO$ or $>CR_3R_4$ where R_3 and R_4 are independently

hydrogen, lower alkyl, lower alkoxy or together form a cyclic acetal;

Z is lower alkyl;

and W represents one or more substituents independently selected from hydrogen, lower alkyl, lower alkoxy or halogen;

stereo and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof, for the manufacture of a medicament for th treatment of conditions such as glaucoma and myasthenia gravis and, more particularly, for the prevention or treatment of cognitive dysfunctions which may be associated with ageing or with conditions such as Alzheimer's Disease, Senile and related Dementias, Parkinson's Disease, Down's Syndrome and Huntington's Chorea.

Moreover, the present invention relates to a method for the treatment of central cholinergic dysfunction wher by a pharmacologically effective amount f a compound

according to claim 1 is administered to a host in need of said treatment.

Pharmacology

The compounds of general formula (1) of the present invention are useful in the treatment of various cognitive dysfunctions, such as those occurring in Alzheimer's disease. This utility is manifested by the ability of these compounds to inhibit the enzyme acetylcholinesterase.

Acetylcholinesterase Inhibition Assay

The ability of compounds in general to inhibit the acetylcholinesterase activity of rat brain homogenate was determined using the spectrophotometric method of Ellman et al, Biochem.Pharmacol., 1961, 7, 88. Results are expressed as IC_{50} nanomolar (i.e. the nanomolar concentration of test compound required to inhibit enzyme activity by 50%).

Further the compounds of this invention potentiate cholinergic function in the brain such that when administered to rodents these compounds induce marked cholinergic effects such as tremor. These utilities are further demonstrated by the ability of these compounds to restore cholinergically deficient memory in a delayed non-matched to sample task.

Delayed Non-Matched to Sample Assay

Rats were trained on a delayed non-matched to sample task similar to that described by Murray et al, Psychopharmacology, 1991, 105, 134-136. Scopolamine, an anticholinergic that is known to cause memory impairment, induces an impairment in performance of this task. This impairment is reversed by compounds of the type described in the present invention.

Pharmaceutical formulations

The administration in the novel method of treatment of this invention may conveniently be oral, rectal, or parenteral at a dosage level of, for example, about 0.0001 to 10 mg/kg, preferably about 0.001 to 1.0 mg/kg and especially about 0.01 to 0.2 mg/kg and may b administered on a regimen of 1 to 4 doses or treatments per day. The dose will depend on the route of administration, a preferred route being by oral administration. It will be appreciated that the severity of the disease, the age of the patient and other factors normally considered by the attending physician will influence the individual regimen and dosage most appropriate for a particular patient.

The pharmaceutical formulations comprising the compound of this invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral solutions or suspensions for parenteral administration; or as suppositories for rectal administration; or as suitable topical formulations. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described, for example, in "Pharmaceuticals - The Science of Dosage Form Design", M.E. Aulton, Churchill Livingstone, 1988.

To produce pharmaceutical formulations containing a compound according to the present invention in the form of dosage units for oral application the active substance may be admixed with an adjuvant/a carrier e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets.

If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a polymer known to the man skilled in the art, dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different active substances or different amounts of the active compounds.

For the preparation of soft gelatine capsules, the active substance may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the active substance using either the above-mentioned excipients for tablets e.g. lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine. Also liquids or semisolids of the drug can be filled into hard gelatine capsules.

Dosage units for rectal application can be solutions or suspensions or can be prepared in the form of suppositories comprising the active substance in admixture with a neutral fatty base, or gelatine rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing from about 0.02% to about 20% by weight of the active substance herein described, the balance being sugar and mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to the man in the art.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance, preferably in a concentration of from about 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

EXAMPLE 1

5-Cyclohexyl-1,3-dihydro-2H-indol-2-one

5-Cyclohexyl-1H-indole-2,3-dione (3.4 g) in methanol (100 ml) was treated with 1,2-ethanedithiol (1.5 g) and boron trifluoride diethyletherate (2 ml). The mixture was stirred at room temperature overnight and then evaporated to dryness under reduced pressure. The residue was purified by flash chromatography to yield the corresponding dithioacetal. This material in ethanol (100 ml) was treated with Raney nickel (50% slurry in water, 40 g) and the mixture was heated under reflux overnight. The mixture was filtered through Celite and the residues washed thoroughly with ethanol. The combined filtrates were evaporated to give the title compound as a white solid (2.9 g, 88%), m.p. 153-155°C. ^{1}H Nmr (d_6-DMSO) 1.2-1.5 (5H, m), 1.7-2.0 (5H, m), 2.5 (1H, m), 3.5 (2H, s), 6.8 (1H, d), 7.08 (1H, dd) and 7.15 (1H, d) ppm.

EXAMPLE 2

1-(5-Bromopentyl)-1,3-dihydro-2H-indol-2-one

1,3-Dihydro-2H-indol-2-one (13.3g), 1,5-dibromopentane (46g) and anhydrous potassium carbonate (17g) in acetonitrile (200ml) were heated under reflux for 24 hours. The mixture was filtered. The filtrate was evaporated t dryness and the residue thus obtained was purified by flash chromatography to give the title compound as an oil.

^{1}H Nmr ($CDCl_3$) 1.51, 1.7 and 1.9 (ach 2H, m), 3.37 (2H, t), 3.5 (2H, s), 3.7 (2H, t), 6.82 (1H, d), 7.03 (1H, t) and 7.25 (2H, m) ppm.

^{13}C Nmr ($CDCl_3$) 25.3, 26.7, 32.1, 33.0, 35.5, 39.4, 108.0, 122.0, 124.3, 124.5, 127.6, 144.3 and 174.7 ppm.

Using the appropriate starting materials and following the general method of Example 2 the compounds of Examples 3 to 5 were prepared.

EXAMPLE 3

1-(4-Bromobutyl)-1,3-dihydro-2H-indol-2-one

^{1}H Nmr ($CDCl_3$) 1.9 (4H, m), 3.42 (2H, t), 3.5 (2H, s), 3.74 (2H, t), 6.83 (1H, d), 7.02 (1H, t) and 7.25 (2H, m) ppm.

EXAMPLE 4

1-(6-Bromohexyl)-1,3-dihydro-2H-indol-2-one

^{13}C Nmr ($CDCl_3$) 25.6, 26.8, 27.3, 32.1, 33.2, 35.2, 39.3, 107.8, 121.6, 124.0, 124.2, 127.3, 144.0 and 174.4 ppm.

EXAMPLE 5

1-(5-Bromopentyl)-1,3-dihydro-5-cyclohexyl-2H-indol-2-one

^{13}C Nmr ($CDCl_3$) 25.5, 26.1, 26.7, 26.9, 32.3, 33.3, 34.8, 35.9, 39.7, 44.3, 107.9, 123.2, 124.7, 125.9, 142.4 and 175.0 ppm.

EXAMPLE 6

5'-Cyclohexyl-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

5-Cyclohexyl-1H-indole-2,3-dione (1 equivalent), ethane-1,2-diol (5 equivalents) and p-toluenesulphonic acid (0.02 equivalents) in dry toluene wer heat d und r reflux ov rnight with azeotropic removal of water. The reaction mixtur was cooled, washed with saturated sodium

bicarbonate solution, and then worked up in the usual manner to afford the title compound.
M.p. 178-180°C.
^{13}C Nmr ($CDCl_3$) 175.8, 143.4, 139.6, 129.9, 124.1, 123.4, 110.5, 102.6, 65.7, 44.1, 34.5, 26.8 and 26.0 ppm.

EXAMPLE 7

1'-(6-Bromohexyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)one

Spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one (5.12g), 1,6-dibromohexane (12.2g) and anhydrous potassium carbonate (6.9g) in acetone (200ml) were heated under reflux for 24 hours. The mixture was filtered. The filtrate was evaporated to dryness and the residue thus obtained was purified by flash chromatography to give the title compound as an oil.

^{13}C Nmr ($CDCl_3$) 25.7, 26.8, 27.5, 32.3, 33.4, 39.2, 65.6, 101.9, 108.6, 122.8, 124.0, 124.7, 131.4, 143.8 and 173.0 ppm.

Using the appropriate starting materials and following the general method of Example 7 the compounds of Examples 8 to 10 were prepared.

EXAMPLE 8

1'-(4-Bromobutyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

^{13}C Nmr ($CDCl_3$) 25.4, 29.3, 32.7, 38.2, 65.5, 101.7, 108.5, 122.8, 123.9, 124.6, 131.3, 143.5 and 173.0 ppm.

EXAMPLE 9

1'-(5-Bromopentyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

^{13}C Nmr ($CDCl_3$) 25.1, 26.2, 32.0, 33.1, 39.1, 65.6, 101.8, 108.6, 122.9, 123.9, 124.7, 131.4, 143.7 and 173.0 ppm.

EXAMPLE 10

1'-(5-Bromopentyl)-5'-cyclohexyl-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

^{13}C Nmr ($CDCl_3$) 25.2, 25.9, 26.3, 26.7, 32.1, 33.0, 34.4, 39.2, 44.0, 65.6, 102.2, 108.4, 123.3, 123.8, 129.6, 141.7, 143.2 and 173.2 ppm.

EXAMPLE 11

1,3-Dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-2H-indol-2-one

1-(5-Bromopentyl)-1,3-dihydro-2H-indol-2-one (8g) and N-ethyl-N-phenylmethylamine (12.15g) in dichloromethane (150ml) were heated under reflux for 24 hours. The mixture was evaporated to dryness and the residue was purified by flash chromatography to give the title compound.

^{13}C Nmr ($CDCl_3$) 11.6, 24.6, 26.6, 27.2, 35.6, 39.8, 47.2, 52.8, 58.0, 108.1, 121.9, 124.2, 124.5, 126.5, 127.6, 127.9, 128.6, 140.0, 144.5 and 174.7 ppm.

$m/_z$ 337 ($M + H^+$)

The corresponding fumarate was prepared using fumaric acid in methanol.

^{13}C Nmr ($CDCl_3$) 9.0, 23.4, 24.1, 26.9, 35.7, 39.4, 45.9, 50.8, 55.7, 108.4, 122.2, 124.4, 124.5, 127.9, 128.9, 130.5, 131.4, 135.3, 144.3, 170.4 and 175.1 ppm.

Using the appropriate starting material and following the general method of Example 11 the compounds of Examples 12 to 14 were prepared.

EXAMPLE 12

1,3-Dihydro-1-(4-(N-ethyl-N-phenylmethylamino)butyl)-2H-indol-2-one

^{13}C Nmr ($CDCl_3$) 11.6, 24.4, 25.0, 35.5, 39.6, 47.1, 52.5, 57.9, 108.1, 121.8, 124.2, 124.4, 126.5, 127.5, 127.9, 128.6, 139.8, 144.4 and 174.6 ppm.

$m/_z$ 323 ($M + H^+$)

Fumarate, ^{13}C Nmr ($CDCl_3$) 9.6, 22.1, 25.0, 35.7, 39.3, 46.2, 51.2, 56.4, 108.4, 122.3, 124.4, 124.5, 127.9, 128.4, 128.7, 130.1, 133.3, 135.3, 144.2, 170.4 and 175.1 ppm.

EXAMPLE 13

1,3-Dihydro-1-(6-(N-ethyl-N-phenylmethylamino)hexyl)-2H-indol-2-one

^{13}C Nmr ($CDCl_3$) 11.7, 26.8, 26.9, 27.0, 27.4, 35.7, 39.9, 47.2, 53.0, 58.0, 108.2, 121.9, 124.3, 124.6, 126.5, 127.7, 128.0, 128.7, 140.1, 144.6 and 174.8 ppm.

$m/_z$ 351 ($M + H^+$)

Fumarate, ^{13}C Nmr ($CDCl_3$) 8.7, 23.1, 26.3, 27.1, 29.5, 35.7, 39.6, 45.7, 50.3, 55.4, 108.3, 122.1, 124.3, 124.5, 127.8, 128.9, 129.1, 130.5, 130.6, 135.2, 144.4, 170.3 and 175.1 ppm.

EXAMPLE 14

5-Cyclohexyl-1,3-dihydro-1-(5-(N-ethyl-N-phenylmethyl-amino)pentyl)-2H-indol-2-one

^{13}C Nmr ($CDCl_3$) 11.7, 24.7, 26.0, 26.7, 26.8, 27.3, 34.7, 35.8, 39.9, 44.2, 47.2, 52.9, 58.0, 108.0, 123.0, 124.6, 125.8, 126.5, 128.0, 128.7, 140.0, 142.1, 142.5 and 174.8 ppm.

$m/_z$ 419 ($M + H^+$)

Fumarate, ^{13}C Nmr (d_6-DMSO) 10.6, 23.8, 25.1, 25.5, 26.3, 26.7, 34.2, 35.1, 43.4, 46.5, 51.8, 56.8, 107.9, 122.6, 124.6, 125.4, 127.1, 128.1, 128.9, 134.2, 137.4, 141.1, 142.2, 166.5 and 174.1 ppm.

EXAMPLE 15

1'-(4-(N-Ethyl-N-phenylmethylamino)butyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

1'-(4-Bromobutyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one (6g), N-ethyl-N-phenylmethylamine (5.13g) and anhydrous potassium carbonate (10.5g) in acetonitrile (150ml) were heated under reflux for 24 hours. The mixture was filtered. The filtrate was evaporated to dryness and the residue was purified by flash chromatography to afford the title compound.

^{13}C Nmr ($CDCl_3$) 11.7, 24.3, 24.9, 39.5, 47.2, 52.4, 58.0, 65.7, 102.1, 108.9, 122.9, 124.1, 124.8, 126.6, 128.0, 128.7, 131.5, 140.0, 144.1 and 173.2 ppm.

Using the appropriate starting material and following the general method of Example 15 the compounds of Examples 16 to 18 were prepared.

EXAMPLE 16

1'-(5-(N-Ethyl-N-phenylmethylamino)pentyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

^{13}C Nmr ($CDCl_3$) 11.7, 24.6, 26.6, 27.1, 39.6, 47.2, 52.9, 58.1, 65.7, 102.1, 108.8, 122.9, 124.1, 124.8, 126.6, 128.0, 128.7, 131.5, 140.0, 144.1 and 173.2 ppm.

EXAMPLE 17

1'-(6-(N-Ethyl-N-phenylmethylamino)hexyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

^{13}C Nmr ($CDCl_3$) 11.6, 26.6, 26.7, 26.9, 27.0, 39.5, 47.1, 52.9, 57.9, 65.6, 102.0, 108.7, 122.8, 124.0, 124.7, 126.4, 127.9, 128.6, 131.4, 140.0, 144.0 and 173.0 ppm.

EXAMPLE 18

5'-Cyclohexyl-1'-(5-(N-ethyl-N-phenylmethylamino) pentyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

EXAMPLE 19

1-(4-(N-Ethyl-N-phenylmethylamino)butyl)-1H-indole-2,3-dione

1'-(4-(N-Ethyl-N-phenylmethylamino)butyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one (5.8g) in tetrahydrofuran (150ml) containing conc hydrochloric acid (4ml) and water (16ml) was heated under reflux overnight. The organic solvent was removed. The residue was basified by the addition of sodium carbonate solution and then extracted with dichloromethane. The extracts were dried and evaporated and the residue was purified by flash chromatography to give the title compound.

^{13}C Nmr ($CDCl_3$) 11.6, 24.4, 24.8, 39.9, 47.3, 52.3, 58.0, 110.1, 117.4, 123.4, 125.1, 126.6, 128.0, 128.6, 138.2, 139.7, 150.9, 158.0 and 183.4 ppm.

$m/_z$ 337 ($M + H^+$)

Fumarate, ^{13}C Nmr ($CDCl_3$) 9.3, 22.1, 24.8, 39.6, 46.3, 51.1, 56.2, 110.4, 117.5, 123.8, 125.3, 128.9, 130.3, 135.3, 138.6, 150.6, 158.3, 170.4 and 183.4 ppm.

Using the appropriate starting material and following the general method of Example 19 the compounds of Examples 20 to 22 were prepared.

EXAMPLE 20

1-(5-(N-Ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 11.7, 24.6, 26.7, 27.1, 40.1, 47.3, 52.8, 58.1, 110.1, 117.5, 123.5, 125.3, 126.6, 128.0, 128.7,

138.2, 140.0, 151.0, 158.1 and 183.5 ppm.

$m/_z$ 351 ($M + H^+$)

Fumarate, ^{13}C Nmr ($CDCl_3$) 9.6, 24.2, 24.4, 26.7, 39.8, 46.1, 51.3, 56.3, 110.2, 117.4, 123.6, 125.3, 128.2, 128.6, 130.0, 133.9, 135.5, 138.4, 150.8, 158.1, 170.9 and 183.5 ppm.

EXAMPLE 21

1-(6-(N-Ethyl-N-phenylmethylamino)hexyl)-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 11.6, 26.6, 26.7, 26.8, 27.1, 40.0, 47.1, 52.8, 57.9, 110.0, 117.4, 123.4, 125.1, 126.5, 127.9, 128.6, 138.2, 140.0, 150.9, 157.9 and 183.4 ppm.

Fumarate, ^{13}C Nmr (d_6-DMSO) 11.0, 25.6, 26.2, 26.5, 26.9, 46.8, 52.1, 55.0, 57.1, 110.9, 117.6, 123.3 124.6, 127.4, 128.4, 129.2, 134.6, 137.8, 138.4, 151.0, 158.2, 167.0 and 183.7 ppm.

EXAMPLE 22

5-Cyclohexyl-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 11.7, 24.7, 25.9, 26.6, 26.7, 27.2, 34.3, 40.2, 43.7, 47.4, 52.9, 58.1, 109.9, 117.7, 123.6, 126.7, 128.1, 128.7, 136.8, 140.0, 143.8, 149.1, 158.3 and 183.9 ppm.

$m/_z$ 433 ($M + H^+$)

EXAMPLE 23

1,3-Dihydro-1-(5-(N-methyl-N-phenylmethylamino)pentyl)-2H-indol-2-one

The title compound was prepared using the general method of Example 11 but employing N-methyl-N-phenylmethylamine.

^{13}C Nmr ($CDCl_3$) 24.5, 26.8, 27.1, 35.5, 39.7, 42.0, 56.9,

62.2, 108.0, 121.8, 124.2, 124.4, 126.6, 127.5, 127.9, 128.6, 139.1, 144.4 and 174.6 ppm.

EXAMPLE 24

1,3-Dihydro-1-(5-(N-ethyl-N-(4-fluorophenyl) methylamino)pentyl-2H-indol-2-one

The title compound was prepared using the general method of Example 11 but employing N-ethyl-N-(4-fluorophenyl) methylamine.

^{13}C Nmr ($CDCl_3$) 11.5, 24.5, 26.5, 27.0, 35.4, 39.6, 47.0, 52.6, 57.1, 107.8, 114.9(d), 121.8, 123.5, 124.3, 127.4, 129.8(d), 135.5(d), 144.3, 159.7 and 163.3(d), and 174.5 ppm.

EXAMPLE 25

1,3-Dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-5-methyl-2H-indol-2-one

1,3-Dihydro-5-methyl-2H-indol-2-one and 1,5-dibromopentane were reacted together according to the general method of Example 2. The crude 1-(5-bromopentyl)-1,3-dihydro-5-methyl-2H-indol-2-one thus obtained was then reacted with N-ethyl-N-phenylmethylamine according to the method of Example 11 to give title compound.

^{13}C Nmr ($CDCl_3$) 11.6, 20.9, 24.7, 26.6, 27.3, 35.7, 39.9, 47.2, 52.9, 58.0, 107.9, 124.7, 125.2, 126.7, 127.8, 128.0, 128.8, 131.5, 139.6, 142.2 and 174.8 ppm.

EXAMPLE 26

1-(5-Bromopentyl)-5-(1-methylethyl)-1H-indole-2,3-dione

5-(1-Methylethyl)-1H-indole-2,3-dione (3.8g), 1,5-dibromopentane (9.2g) and anhydrous potassium carbonate (5.5g) were heated under reflux in acetonitrile overnight. The mixture was filtered. The filtrate was evaporated to dryness and the residue thus obtained was purified by flash chromatography to give the title

compound as a r d oil.

^{13}C Nmr ($CDCl_3$) 23.6, 25.3, 26.4, 32.0, 32.9, 33.4, 39.8, 109.9, 117.7, 123.1, 136.4, 144.7, 148.9, 158.3 and 183.5 ppm.

Using the appropriate starting materials and following the general method of Example 26, the compounds of Examples 27 to 31 were prepared.

EXAMPLE 27

1-(5-Bromopentyl)-5-methoxy-1H-indole-2,3-dione

^{1}H Nmr ($CDCl_3$) 1.45-1.6, 1.65-1.8 and 1.85-2.0 (each 2H, m), 3.4 (2H, t) 3.7 (2H, t), 3.82 (3H, s), 6.85 (1H, d) and 7.1-7.2 (2H, m) ppm.

EXAMPLE 28

5-Bromo-1-(5-bromopentyl)-1H-indole-2,3-dione

^{1}H Nmr ($CDCl_3$) 1.45-1.6, 1.65-1.8 and 1.85-2.0 (each 2H, m) 3.42 (2H, t) 3.75 (2H, t), 6.84 (1H, d) and 7.67-7.74 (2H, m) ppm.

EXAMPLE 29

1-(4-Bromobutyl)-5-cyclohexyl-1H-indole-2,3-dione

M.p. 70-71°C.

^{13}C Nmr ($CDCl_3$) 25.8, 25.9, 26.6, 29.6, 32.7, 34.3, 39.1, 43.7, 109.9, 117.7, 123.7, 136.9, 144.1, 148.7, 158.4 and 183.5 ppm.

EXAMPLE 30

1-(5-Bromopentyl)-5-phenyl-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 25.4, 26.9, 32.1, 33.0, 40.1, 110.3, 118.1, 123.9, 126.5, 127.9, 129.0, 136.7, 137.3, 139.0, 149.9, 158.3 and 183.4 ppm.

EXAMPLE 31

1-(4-Bromobutyl)-5-phenyl-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 25.8, 29.6, 32.6, 39.3, 110.4, 118.0, 123.9, 126.5, 127.9, 129.0, 136.8, 137.3, 138.9, 149.7, 158.3 and 183.4 ppm.

EXAMPLE 32

5-Cyclohexyl-1-(4-(N-ethyl-N-phenylmethylamino)butyl)-1H-indole-2,3-dione

1-(4-Bromobutyl)-5-cyclohexyl-1H-indole-2,3-dione (4.6g), N-ethyl-N-phenylmethylamine (1.9g) and triethylamine (1.3g) were heated under reflux in acetonitrile overnight. The mixture was evaporated to dryness and the residue was purified by flash chromatography on silica gel to give the title compound as a red oil.

^{13}C Nmr ($CDCl_3$) 11.7, 24.6, 25.0, 25.9, 26.6, 34.3, 40.0, 43.7, 47.4, 52.3, 58.2, 110.0, 117.7, 123.5, 126.7, 128.1, 128.7, 136.8, 140.0, 143.8, 149.1, 158.3 and 183.9 ppm.

Fumarate, M.p. 116-120°C.

^{13}C Nmr (d_6-DMSO) 12.0, 24.2, 25.4, 26.2, 27.0, 34.5, 39.3, 43.6, 47.5, 52.8, 58.0, 111.4, 118.2, 123.2, 127.6, 128.9, 129.5, 135.0, 137.3, 139.7, 143.6, 149.7, 158.9, 167.1 and 184.5 ppm.

Using the appropriately substituted 1H-indole-2,3-dione and the appropriate amine and following the general method of Example 32, the compounds of Examples 33 to 38 were prepared.

EXAMPLE 33

1-(5-(N-Ethyl-N-phenylmethylamino)pentyl)-5-(1-methylethyl)-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 11.7, 23.6, 24.5, 26.7, 27.0, 33.3, 40.1,

47.3, 52.8, 58.1, 109.9, 117.7, 123.0, 126.5, 127.9, 128.6, 136.3, 140.0, 144.4, 149.1, 158.2 and 183.6 ppm.

EXAMPLE 34

1-(5-(N-Ethyl-N-phenylmethylamino)pentyl)-5-methoxy-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 11.6, 24.4, 26.6, 27.1, 39.8, 47.2, 52.7, 55.7, 58.0, 109.5, 110.9, 117.9, 124.2, 126.4, 127.8, 128.2, 140.0, 144.7, 156.2, 157.9 and 183.6 ppm.

EXAMPLE 35

1-(4-(N-Ethyl-N-phenylmethylamino)butyl)-5-phenyl-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 11.6, 24.4, 24.9, 40.0, 47.3, 52.4, 58.0, 110.5, 117.9, 123.5, 126.3, 126.6, 127.7, 128.0, 128.6, 128.9, 136.5, 136.8, 138.8, 139.8, 149.9, 158.0 and 183.5 ppm.

EXAMPLE 36

1-(5-(N-Methyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 24.3, 26.6, 26.8, 39.8, 41.8, 56.6, 62.1, 109.9, 117.2, 123.2, 124.8, 126.5, 127.8, 128.5, 138.0, 139.0, 150.7, 157.8 and 183.2 ppm.

Fumarate, M.p. 134-136°C.

^{13}C Nmr (d_6-DMSO) 23.8, 25.3, 26.4, 38.7, 40.8, 55.8, 60.6, 110.6, 117.3, 123.0, 124.3, 127.3, 128.1, 129.1, 134.1, 136.7, 138.1, 150.7, 157.9, 166.3 and 183.4 ppm.

EXAMPLE 37

1-(5-(N-Ethyl-N-phenylmethylamino)pentyl)-5-phenyl-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 11.8, 24.7, 26.8, 27.2, 40.3, 47.5, 52.9, 58.2, 110.4, 117.5, 123.7, 126.5, 126.6, 127.8, 128.0, 128.7, 129.0, 136.6, 137.1, 139.2, 140.5, 150.1, 158.2 and 183.6 ppm.

Fumarate

Found: C, 68.2; H, 6.2; N, 4.9. $C_{28}H_{30}N_2O_2 \cdot C_4H_4O_2 \cdot H_2O$ requires C, 68.6; H, 6.5; N, 5.0%

EXAMPLE 38

5-Bromo-1-(5-N-ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione

^{13}C Nmr ($CDCl_3$) 11.7, 24.6, 26.8, 26.9, 40.3, 47.4, 52.8, 58.2, 111.8, 116.2, 118.8, 126.6, 127.8, 128.0, 128.6, 140.1, 140.3, 149.7, 157.3 and 182.3 ppm.

EXAMPLE 39

5'-(1-Piperidinyl)-spiro-[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

5-Amino-spiro [1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one (2.04g) and sodium borohydride (1.5g) in dimethoxyethane (20ml) were cooled and glutaric dialdehyde (25% solution in water, 6ml) in a mixture of dimethoxyethane (30ml), methanol (20ml) and 3M sulphuric acid (15ml) was added such that the temperature was maintained in the range -5 to 0°C. More sodium borohydride (1.5g) was then added, maintaining the same temperature range. The mixture was allowed to warm to room temperature and after 2 hours was neutralised and then extracted with dichloromethane. Flash chromatography of the material thus obtained gave the title compound.

m/z 275 ($M + H^+$)

^{13}C Nmr ($CDCl_3$) 24.1, 25.9, 51.9, 65.7, 102.7, 110.9, 115.0, 120.3, 124.9, 134.3, 149.5 and 175.5 ppm.

EXAMPLE 40

1'-(5-Bromopentyl)-5'-(1-piperidinyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

The product from Example 39 was treated by the general method of Example 7 to give the title compound.

^{13}C Nmr ($CDCl_3$) 23.9, 25.1, 25.7, 26.2, 31.9, 33.0, 39.1,

51.5, 65.5, 102.3, 108.9, 114.8, 119.4, 124.6, 136.1, 149.2 and 172.9 ppm.

EXAMPLE 41

1'-(5-(N-Ethyl-N-phenylmethylamino)pentyl)-5'-(1-piperidinyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

The product from Example 40 was treated by the general method of Example 15 to give the title compound.

^{13}C Nmr ($CDCl_3$) 11.6, 23.9, 24.4, 25.8, 26.5, 26.9, 39.4, 47.1, 51.6, 52.8, 57.9, 65.4, 102.3, 108.9, 114.8, 119.4, 124.5, 126.3, 127.8, 128.5, 136.4, 140.0, 149.1 and 172.9 ppm.

EXAMPLE 42

1-(5-(N-Ethyl-N-phenylmethylamino)pentyl)-5-(1-piperidinyl)-1H-indole-2,3-dione

The product from Example 41 was treated by the general method of Example 19 to give the title compound.

^{13}C Nmr ($CDCl_3$) 11.7, 23.9, 24.7, 25.7, 26.8, 27.2, 40.1, 47.4, 51.2, 52.9, 58.2, 110.6, 113.6, 118.1, 126.3, 126.6, 128.1, 128.7, 140.1, 143.5, 149.3, 158.3 and 183.8 ppm.

EXAMPLE 43

5'-Iodo-spiro[1,3-dioxane-2,3'-[3H]-indol]-2'(1'H)-one

5-Iodo-1H-indole-2,3-dione and propane-1,3-diol were treated according to the general method of Example 6 to give the title compound.

^{13}C Nmr ($CDCl_3$) 25.2, 61.2, 85.5, 93.4, 112.1, 129.8, 133.3, 139.6, 139.7 and 173.3 ppm.

EXAMPLE 44

1'-(5-Bromopentyl)-5'-iodo-spiro[1,3-dioxane-2,3'-[3H]-indol]-2'(1'H)-one

The product from Example 43 and 1,5-dibromopentane were treated according to the general method of Example 7 to give the title compound.

^{13}C Nmr ($CDCl_3$) 25.1, 25.2, 26.2, 32.0, 33.2, 39.0, 61.2, 85.3, 93.0, 110.4, 129.3, 133.0, 139.4, 141.9 and 170.8 ppm.

EXAMPLE 45

1'-(5-(N-Ethyl-N-phenylmethylamino)pentyl)-5'-iodo-spiro[1,3-dioxane-2,3'-[3H]-indol]-2'(1'H)-one

The product from Example 44 was treated according to the general method of Example 15 to give the title compound.

^{13}C Nmr ($CDCl_3$) 11.7, 24.4, 25.1, 26.5, 26.8, 39.1, 47.2, 52.7, 58.0, 60.9, 85.0, 92.9, 110.3, 126.4, 127.9, 128.5, 129.3, 132.8, 139.2, 140.0, 142.0 and 170.6 ppm.

EXAMPLE 46

1'-(5-Bromopentyl)-5'-nitro-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

5'-Nitro-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-on and 1,5-dibromopentane were treated according to th general method of Example 7 to give the title compound.

^{13}C Nmr ($CDCl_3$) 25.1, 26.2, 31.9, 33.0, 39.7, 66.0, 100.7, 108.5, 120.9, 125.2, 128.2, 143.6, 149.4 and 173.2 ppm.

EXAMPLE 47

1'-(5-(N-Ethyl-N-phenylmethylamino)pentyl)-5'-nitro-spiro[1,3-diox lane-2,3'-[3H]-indol]-2'(1'H)-one

The product from Exampl 46 was treated according to the general meth d of Example 15 to give the title compound.

^{13}C Nmr ($CDCl_3$) 11.6, 24.3, 26.5, 26.8, 39.9, 47.2, 52.6, 58.0, 65.9, 100.7, 108.4, 120.7, 125.1, 126.4, 127.8, 128.1, 128.5, 140.0, 143.4, 149.6 and 173.1 ppm.

EXAMPLE 48

5'-Amino-1'-(5-(N-ethyl-N-phenylmethylamino)pentyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

The product from Example 47 and 10% palladium on activated carbon in ethanol were shaken under an atmosphere of hydrogen at room temperature overnight. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue thus obtained was purified by flash chromatography to yield the title compound.

^{13}C Nmr ($CDCl_3$) 11.5, 24.5, 26.5, 27.0, 39.5, 47.1, 52.8, 57.9, 65.6, 102.3, 109.4, 112.6, 116.9, 125.1, 126.5, 127.9, 128.6, 135.5, 139.8, 142.7 and 172.7 ppm.

EXAMPLE 49

5'-Acetamido-1'-(5-(N-ethyl-N-phenylmethylamino)pentyl)-spiro[1,3-dioxolane-2,3'-[3H]-indol]-2'(1'H)-one

The product from Example 48 (4.9g), acetyl chloride (1.9g) and triethylamine (4.8g) in dichloromethane were stirred overnight at room temperature. The reaction mixture was washed with sodium hydrogen carbonate solution, dried and evaporated to dryness. The residue was purified by flash chromatography on silica gel to give the title compound.

M.p. 137-139°C.

^{13}C Nmr (d_6-DMSO) 11.5, 23.7, 23.9, 26.0, 26.4, 38.9, 46.5, 52.2, 57.4, 65.4, 101.3, 109.3, 116.3, 122.0, 124.0, 126.3, 127.8, 128.3, 134.8, 138.8, 139.9, 167.9 and 172.3 ppm.

EXAMPLE 50

5-Cyclohexyl-1,3-dihydro-1-(4-(N-ethyl-N-phenylmethyl-amino)butyl)-2H-indol-2-one

The product from Example 32 (2.4g), 1,2-ethanedithiol (0.6ml) and p-toluenesulphonic acid (2.2g) were stirred overnight at room temperature in glacial acetic acid. The mixture was evaporated to dryness and the residue was further processed as in Example 1 to give the intermediate dithioacetal and thence the title compound.

^{13}C Nmr ($CDCl_3$) 11.7, 24.5, 25.1, 26.0, 27.0, 34.8, 35.8, 40.0, 44.3, 47.2, 52.7, 58.0, 108.1, 123.1, 124.7, 125.9, 126.7, 128.1, 128.8, 140.0, 142.2, 142.6 and 175.0 ppm.

EXAMPLE 51

1,3-Dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-5-(1-methylethyl)-2H-indol-2-one

Using the general method of Example 50, the product of Example 33 was converted into the title compound.

^{13}C Nmr ($CDCl_3$) 11.6, 24.1, 24.7, 26.7, 27.3, 33.7, 35.8, 39.9, 47.2, 52.9, 58.0, 107.9, 122.5, 124.6, 125.3, 126.5, 127.9, 128.6, 140.0, 142.5, 142.8 and 174.8 ppm.

EXAMPLE 52

1,3-Dihydro-1-(5-(N-ethylamino)pentyl)-5-phenyl-2H-indol-2-one

Using the general method of Example 50 but using tert-butanol rather than ethanol as the solvent for the second step, the product of Example 37 gave the title compound. M.p. 214-215°C.

^{13}C Nmr (d_6-DMSO) 10.8, 23.2, 25.0, 26.4, 35.1, 41.6, 45.9, 108.6, 122.7, 125.4, 125.9, 126.1, 126.6, 128.7, 133.9, 140.1, 143.7 and 174.2 ppm.

EXAMPLE 53

1,3-Dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-5-phenyl-2H-indol-2-one

The product from Example 52 (500mg), benzyl bromide (300mg) and anhydrous potassium carbonate (660mg) were stirred in dry dimethylformamide at room temperature to give the title compound.

^{13}C Nmr ($CDCl_3$) 11.8, 24.8, 27.1, 27.4, 35.8, 40.1, 47.4, 53.0, 58.2, 108.4, 123.4, 125.2, 126.5, 126.6, 126.8, 128.0, 128.6, 128.7, 135.6, 140.1, 140.9, 144.1 and 174.8 ppm.

EXAMPLE 54

1,3-Dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-5-methoxy-2H-indol-2-one

Using the general method of Example 50, the product of Example 34 was converted into the title compound.

^{13}C Nmr ($CDCl_3$) 11.7, 24.7, 26.7, 27.3, 36.1, 40.0, 47.3, 53.0, 55.8, 58.1, 108.4, 111.9, 112.1, 125.9, 126.6, 128.0, 128.7, 138.2, 140.1, 155.6 and 174.4 ppm.

PHARMACY EXAMPLES

The following examples illustrate suitable pharmaceutical compositions to be used in the method of the invention.

Composition 1 - Tablets

Compound of Example 14	2g
Lactose	98g
Microcrystalline cellulose	90g
Polyvinylpyrrolidone	8g
Magnesium stearate	2g

The compound of Example 14, lactose, cellulose and polyvinylpyrrolidone are sieved and blended. The magnesium st arate is sieved and then blended into the abov mixture. Compression using suitable punches then

yields 1000 tablets each containing 2mg of the activ ingredient. If desired, the obtained tablets can then be film coated.

Composition 2 - Tablets

Compound of Example 42	20g
Lactose	90g
Microcrystalline cellulose	30g
Potato starch	50g
Polyvinylpyrrolidone	8g
Magnesium stearate	2g

The compound of Example 42, lactose, cellulose and part of the starch are mixed and granulated with 10% starch paste. The resulting mixture is dried and blended with the remaining starch, the polyvinylpyrrolidone and th sieved magnesium stearate. The resulting blend is then compressed to give 1000 tablets each containing 20mg of the active ingredient.

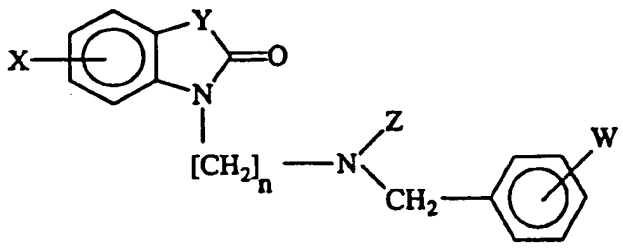
Composition 3 - Capsules

Compound of Example 53	10g
Pregelatinised starch	188g
Magnesium stearate	2g

The compound of Example 53 and the starch are sieved, blended together and then lubricated with the sieved magnesium stearate. The blend is used to fill 1000 hard gelatine capsules of a suitable size. Each capsule contains 10mg of the active ingredient.

CLAIMS

1. A compound having the general formula (1)



(1)

wherein:

n is 3, 4, 5, 6 or 7;

X represents one or more substituents independently selected from hydrogen, lower alkyl, aryl, lower alkoxy, halogen, trifluoromethyl, nitro, -NHCOR where R is lower alkyl or aryl, $-NR_1R_2$ where R_1 and R_2 are independently hydrogen or lower alkyl or together form a ring, or cycloalkyl, cycloalkenyl or bicycloalkyl either optionally further substituted by lower alkyl;

Y is $>CO$ or $>CR_3R_4$ where R_3 and R_4 are independently

hydrogen, lower alkyl, lower alkoxy or together form a cyclic acetal;

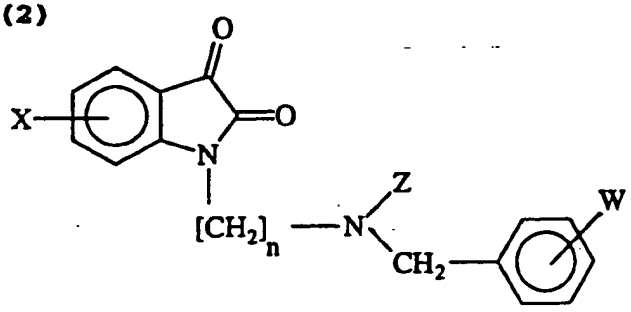
Z is lower alkyl;

and W represents one or more substituents independently selected from hydrogen, lower alkyl, lower alkoxy or halogen;

stereo and optical isomers and racemates thereof where such isomers exist, as well as pharmac utically

acceptable acid addition salts thereof and solvates thereof.

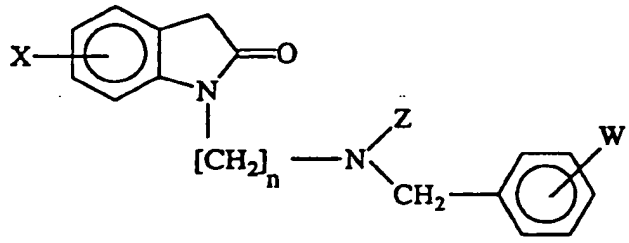
2. A compound according to claim 1 having the general formula (2)



(2)

wherein n, X, W and Z are as defined in claim 1.

3. A compound according to claim 1 having the general formula (3)



(3)

wherein n, X, W and Z are as defined in claim 1.

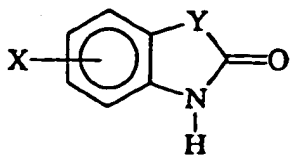
4. A compound according to either of claims 2 or 3 wherein
n is 4, 5 or 6;
W is hydrogen or F; and
X is lower alkyl, lower alkoxy, cycloalkyl, F, aryl, or $-NR_1R_2$ where R_1 and R_2 are independently hydrogen or lower alkyl or together form a ring.

5. A compound according to claim 4 wher in
X is methyl, thyl, methoxy, thoxy, C_5 to C_7 cycloalkyl, F, aryl, especially phenyl, or $-NR_1R_2$, esp cially 1-pyrrolidinyl or 1-piperidinyl.

6. A compound according to claim 1 being:
1,3-dihydro-1-(4-(N-ethyl-N-phenylmethylamino)butyl)-2H-indol-2-one;
5-cyclohexyl-1,3-dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-2H-indol-2-one;
5-cyclohexyl-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione;
1,3-dihydro-1-(5-(N-ethyl-N-(4-fluorophenyl) methylamino)pentyl-2H-indol-2-one;
5-cyclohexyl-1-(4-(N-ethyl-N-phenylmethylamino)butyl)-1H-indole-2,3-dione;
1-(4-(N-ethyl-N-phenylmethylamino)butyl)-5-phenyl-1H-indole-2,3-dione;
1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-5-(1-piperidinyl)-1H-indole-2,3-dione;
5-cyclohexyl-1,3-dihydro-1-(4-(N-ethyl-N-phenylmethylamino)butyl)-2H-indol-2-one;
1,3-dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-5-phenyl-2H-indol-2-one;
1,3-dihydro-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-5-methoxy-2H-indol-2-one; or

pharmaceutically acceptable acid addition salts or solvates thereof.

7. A process for preparing a compound according to claim 1 by treating a compound of the general formula (4)

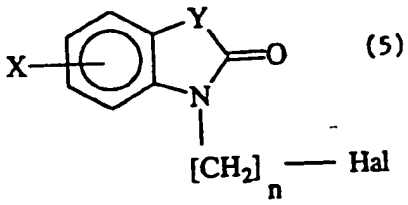


(4)

wherein X and Y are as defined in claim 1,

with a 1,n-dihaloalkane to obtain a compound of the

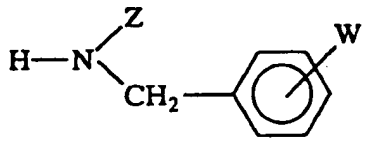
general formula (5)



(5)

wherein X, Y and n are as defined in claim 1 and Hal is halogen,

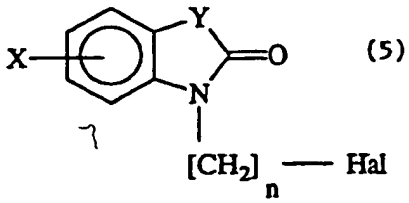
and reacting the compound of the general formula (5) with a compound of the general formula (6)



(6)

wherein W and Z are as defined in claim 1.

8. A compound of general formula (5)



(5)

wherein n is 5, 6 or 7 and X and Y are as defined in claim 1 and Hal is halogen, with the proviso that when n is 5 and Y is >CO then X is not H.

9. A pharmaceutical formulation containing a compound according to claim 1 as active ingredient and a

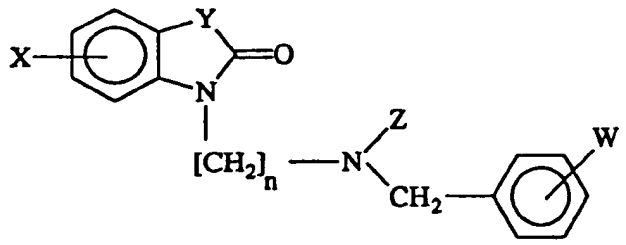
pharmaceutically acceptable carri r.

10. A compound according to claim 1 for use in therapy.

11. A compound as defined in claim 10 for use as an agent for the treatment of conditions which involve a decreased cholinergic function.

12. A compound as defined in claim 10 for use as an agent for prevention or treatment of cognitive dysfunctions.

13. The use of a compound having the general formula (1)



(1)

wherein:

n is 3, 4, 5, 6 or 7;

X represents one or more substituents independently selected from hydrogen, lower alkyl, aryl, lower alkoxy, halogen, trifluoromethyl, nitro, -NHCOR where R is lower alkyl or aryl, $-NR_1R_2$ where R_1 and R_2 are independently hydrogen or lower alkyl or together form a ring, or cycloalkyl, cycloalkenyl or bicycloalkyl either optionally further substituted by lower alkyl;

Y is $>CO$ or $>CR_3R_4$ where R_3 and R_4 are independently hydrogen, lower alkyl, lower alkoxy or tog th r form a cyclic ac tal;

Z is lower alkyl;

and W represents one or more substituents independently selected from hydrogen, lower alkyl, lower alkoxy or halogen;

stereo and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof for the manufacture of a medicament for the treatment of conditions which involve a decreased cholinergic function.

14. The use according to claim 13 for the manufacture of a medicament for the prevention or treatment of cognitive dysfunctions.

15. The use according to claim 13 for the manufacture of a medicament for the treatment of conditions such as glaucoma or myasthenia gravis.

16. The use according to claim 14 for the manufacture of a medicament for the prevention or treatment of cognitive dysfunctions associated with ageing.

17. The use according to claim 14 for the manufacture of a medicament for the prevention or treatment of cognitive dysfunctions associated with conditions such as Alzheimer's Disease, Senile and related Dementias, Parkinson's Disease, Down's Syndrome and Huntington's Chorea.

18. A method for the prevention or treatment of decreased cholinergic function by administering to a host in need of such a treatment a sufficient amount f a c mpound according to claim 1.

19. A method for the prevention or treatment of cognitive dysfunctions by administering to a host in need of such a treatment a sufficient amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00448

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 209/34, C07D 209/38, C07D 491/113, A61K 31/475
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Volume 109, No 9, 29 August 1988 (29.08.88), (Columbus, Ohio, USA), page 680, THE ABSTRACT No 73323m, JP, A, 62294654, (Kissei Pharmaceutical Co., Ltd.) 22 December 1987 (22.12.87), see reg.no. 11555-74-5 and 11555-53-8 --	1-7,9-17
A	CH, A, 491106 (CIBA AKTIENGESELLSCHAFT), 15 July 1970 (15.07.70) --	1-7,9-17

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 1994	09 -11- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00448

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18-19
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see Rule 39.1

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8, 9-17

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/94

International application No.
PCT/SE 94/00448

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH-A- 491106	15/07/70	NONE	